ABSTRACT

The habilitation thesis ***Engineering Bioinspired Hydrogels for Cell-Instructive Scaffolds and Surfaces*** summarizes the main scientific, professional and academic achievements of the candidate in the interval passed from the defence of her PhD thesis, and also describes the research directions envisaged for the future career stage.

The thesis is structured on three sections, Part 1. ***Main scientific, professional, and academic results***, Part 2. ***Future developments*** and Part 3. ***References***.

In the first part, the main research results were selected and overviewed in two chapters, *I.1. The engineering of (bio)functionalized polymers for matricellular interactions* and *I.2. Engineering bioactive or/and nanostructured surfaces and nanocomposites for tissue reconstruction and regeneration*.

Hydrogels are the major building blocks the candidate used in her approaches due to their physico-chemical and mechanical resemblance with the elastic hydrated extracellular matrix (ECM). The development of cell-instructive scaffolds and surfaces was addressed by the candidate through bioconjugation of polymers with cell adhesive peptides or through combination with bioactive ECM-derived biopolymers. An important result was the preparation of alginate-peptide bioconjugates that would further allow to prepare more complex materials by dilution with non-modified polymer, by combination of different bioconjugates or through coating of inert scaffolds. Cells interactions were successfully induced on hydrogels based on such bioconjugates. In addition, new semi-synthetic or hybrid hydrogels were prepared as instructive scaffolds for matricellular interactions. Some methacryloyl derivatives of proteins were used as building blocks to prepare new semi-synthetic materials with improved characteristics over their individual consituents. Hybrids based on methacryloyl gelatin – synthetic polymers present added value when compared to the individual hydrogels, while the correlations composition-properties allow to further prepare scaffolds with predefined features. The biomaterials and protocols developed in these projects opened new research directions including the development of nanocomposites, bioactive coatings and inks for 3D printing.

The other general route to stimulate cell interactions consisted in the development of nanostructured and nanocomposite biomaterials and surfaces as a tool to mimic physical and microstructural properties cells are naturally accustomed with. Cell-interactivity depended on the stimulation of specific biointeractions including cell-adhesiveness and biomineralization; thus, bioinspiration and biomimicry were used to design biomaterials. Extensive characterization of the new systems was performed, and the correlation composition-structure-properties was explored. The investigation of polymer scaffolds seeded with anionic functional groups and of their biomineralization potential was performed. It was noticed for example, that gold nanoparticles surface-decorated with carboxylate functional groups stimulated *in vitro* mineralization in acellular conditions, while they only induced bone tolerance *in vivo*, when nanostructuring the surface of polystyrene fibers. Another interesting finding was that electrospun fibrous gelatin scaffolds loaded with low amount of carboxylated nanodiamond nanoparticles improved cellular interactions. Such nanocomposite microfibers promoted *in vitro* mineralization in cell culture conditions, and stimulated adhesion and proliferation of

MG63 cells and hASCs. Another category of ECM-inspired biomaterials, gelatin-alginate-nanoapatite nanocomposite microparticles, were prepared by a biomimetic method: the nanostructured mineral phase was generated in the organic matrix, through mineralization simultaneously with the crosslinking of the hydrogel precursor. The microparticles were developed as low invasive injectable bone filler with self-assembly ability resulting in an interconnected porosity. The nanostructured surface of such nanocomposites enhanced osteoblasts adhesion, with mineral phase formation *in vitro*, at 7 and 14 days in cell culture. The ability to induce new bone formation *in vivo* was confirmed. These findings open new paths for bone regeneration therapeutic solutions with low-invasive application and no restrictions imposed by the shape of the bone defect.

The candidate presents her future developments plans in the second part of this thesis, reflecting a coherent vision and the commitment to a high-performance research and career.
The main scientific directions comprise **development of complex tissue analogues with hierarchical architecture and predefined properties, development of tissue-mimicking building blocks, engineering cell-biomaterial interface phenomena** and **(nano)composites and nanostructured biomaterials.** The investigation of bioinspired scaffolds with predefined properties for personalized regeneration, better understanding of the role the mechanical sensing has on cellular interactions, the replication of naturally occurring nano-characteristics at mechanical and microstructural levels and personalized design and fabrication are considered to be key strategies for the successful approach of these topics.
These can only be possible with a highly skilled team, internationally competitive.